## Amendments to the Specification:

Please replace existing paragraph **[0015]** on page 4 of the Specification with the following replacement paragraph.

-- **[0015]** ~~Fig. 4 represents~~ Figs. 4A-4C represent the all-atom figure of three peptides: (a) Gly-Gly tripeptide; (b) Me-His-Ser-Me dipeptide with both terminals replaced by methyl groups; and (c) Gly-Ser-Ala-Asp-Val pentapeptide. --

Please replace paragraphs **[0018]**-**[0023]** on pages 4-5 of the Specification with the following replacement paragraphs.

-- **[0018]** ~~Fig. 7 represents~~ Figs. 7A-7F represent one-dimensional (1D) potential curves for triglycine/water interaction at various directions obtained by MFCC and FS calculations using DFT B3LYP/6-31G. The solid line with dots are the FS result, dotted lines are MFCC results and dashed lines are the results from AMBER force fields.

**[0019]** ~~Fig. 8 represents~~ Figs. 8A-8F represent 1D potential curves for Me-His-Ser-Me/water interaction at various directions obtained by MFCC and FS calculations using DFT B3LYP/6-31G. The solid line with dots are the FS result and the dotted lines are MFCC results.

**[0020]** ~~Fig. 9 represents~~ Figs. 9A-9F represent 1D potential curves for Gly-Ser-Ala-Asp-Val/water interaction at various directions obtained by MFCC and FS calculations using HF/3-21G. The solid line with dots are the FS result, the dotted lines are MFCC results, and the dashed lines are the results from AMBER force fields.

**[0021]** ~~Fig. 10 represents~~ Figs. 10A-10F represent 1D potential curves for Gly-Ser-Ala-Asp-Val/water interaction at various directions obtained by MFCC and FS calculations using DFT B3LYP/6-31G. The solid line with dots are the FS result and the dotted lines are MFCC results.

**[0022]** ~~Fig. 11 represents~~ Figs. 11A-11D represent illustrative interaction paths between a water molecule (indicated by arrows) and the fixed structure HIV-1 gp41 protein. The distances is defined between the two atoms on both ends of the arrows except for Fig. 9A where the distance is defined between the oxygen atom of the water and the center-of-mass of gp41.

**[0023]**    ~~Fig. 12 represents~~ Figs. 12A-12D represent the 1D (one-dimensional) gp41-water interaction potential curves as a function of interaction path defined in Fig. 9. The solid circles are the results of ab initio calculations and dotted lines are the results from AMBER force field. The B3LYP/6-31G and MP2/6-31G results are denoted, respectively, by open circles and open squares in (B) and (D). --

Please replace paragraph **[0028]** on page 6 of the Specification with the following replacement paragraph.

-- **[0028]**    The coordinates may then be graphically displayed using a plotting program that displays a molecular image of the molecule in a format such as that shown in ~~Fig. 4 or 5~~ Figs. 4A-4C or Fig. 5. Any VRML compliant program or other program, such as Rasmal™, can be used to perform this function. While it is sometimes easier to conceptualize the features of the molecule when it is visually displayed, it is not necessary to display the molecule for the purposes of this invention. --

Please replace paragraph **[0067]** on page 18 of the Specification with the following replacement paragraph.

-- **[0067]**    The above approach has been tested on a number of peptides interacting with a water molecule and the results of calculations are compared to the full system (FS) *ab initio* calculation. Three different peptides were chosen, as shown in Figs. 4A-C. The first peptide is composed of three glycine (Gly-Gly-Gly) with charged terminals as shown in Fig. 4A. This peptide has a stretched structure whose energy was not optimized. The second peptide is composed of two amino acids but both ends are capped with the methyl group, i.e., Me-His-Ser-Me as shown in Fig. 4B. The structure of this peptide has been optimized using AMBER force field. The third example is a five-base peptide Gly-Ser-Ala-Asp-Val (SEQ ID NO. 1) whose structure has also been optimized using the force field. The interaction energies between these three fixed-structure peptides and a water molecule in gas phase were calculated. The MFCC results were compared with the corresponding full system *ab initio* calculations. All *ab initio* calculations were reported using the Gaussian98 package. --

Please replace paragraphs **[0070]-[0075]** on pages 19-21 of the Specification with the following replacement paragraphs.

-- **[0070]**     More results of calculations for the triglycine/water system at different geometries are shown in Figs. 7A-F. Here the DFT B3LYP/6-31G method has been used for all *ab initio* calculations shown in Figs. 7A-F in both MFCC and full system calculations. In all the six geometries with different approaching spherical angles of water toward peptide, the MFCC results are in excellent agreement with the full system calculations, both in structures and energies of the interaction potential. The largest errors between the MFCC and full system *ab initio* calculations are less than 0.5 kcal/mol in Figs. 7A-F.

**[0071]**     The interaction energies obtained from AMBER force fields for triglycine/water system at the same geometries are also shown in Figs. 7A-F. As shown, the force field gives some reasonable minimum energy positions at these geometries. However, the force field does not give accurate energies. For example, in the potential curve with the spherical angle (90, 0) in Figs. 7A-F, the minimum energy given by the force field is only about 7 kcal/mol compared to the *ab initio* energy of 13 kcal/mol. In another potential with the approaching angle of (120, 60) in Figs. 7A-F, the well depth given by the force field is only about 0.3 kcal/mol compared to the *ab initio* calculation of 2.9 kcal/mol. Similar comparisons are seen for other potential curves in Figs. 7A-F. Thus for the triglycine/water interaction, the force field generally gives energy minimums much higher than *ab initio* calculations.

**[0072]**     For the second system of Me-His-Ser-Me in Figs. 8A-F, the dipeptide His-Ser has two methyl groups at the ends. The interaction potential energy curves are calculated for various approaching spherical angles of the water molecule toward the peptide. The comparison between the MFCC and full system calculations at B3LYP/6-31G level is given in Figs. 8A-F. The results in Figs. 8A-F show that both the structures and energies from the MFCC calculation are in excellent agreement with the results from the full system calculation. Even very shallow wells are accurately reproduced by the MFCC calculation. As shown in Figs. 7A-F, the approaching angle of water at (130,10) exhibiting a well of less than 1 kcal/mol is accurately reproduced by the MFCC calculation. Both attractive and repulsive potentials are correctly reproduced by the MFCC calculation.

**[0073]**     The third system tested is a relatively larger peptide with five amino acids having the sequence: Gly-Ser-Ala-Asp-Val (SEQ ID NO. 1) with charged terminals. This

pentapeptide was specifically chosen to include all three types of side chains: the polar (Ser), nonpolar (Ala and Val) and charged (Asp) side chains and glycine (Gly). In addition, both the N- and C-terminals are charged. This pentapeptide/water system has a total number of 62 atoms. Figures 9A-F shows various 1D potential curves generated from *ab initio* calculations at the HF/3-21G level for different approaching angles of water. The agreement between the MFCC and full system *ab initio* calculations is generally very good for all potential curves as shown in Figs. 9A-F. Both the structures of the potential curves and energies are quite well reproduced by MFCC calculations in all six cases. The largest deviation in energy from the full system calculation is about 0.5 kcal/mol in Figs. 9A-F for the approaching angle of (140, 200). Even the structure of a small bump of about 0.4 kcal/mol for the water approaching angle (30, 240) is faithfully reproduced as shown in Figs. 9A-F. For purpose of comparison, the potential curves obtained from the force field are also shown in Figs. 9A-F. Similar to the results of the triglycine in Figs. 7A-F, the force field generally gives too shallow wells relative to *ab initio* calculations. Next, the DFT calculations were performed at the B3LYP/6-31G level for the same geometries of pentapeptide/water system; the results are shown in Figs. 10A-F. Although there are differences in results between HF/3-21G and B3LYP/6-31G calculations, the MFCC calculation can reproduce the corresponding result of full system calculations using the same level of *ab initio* methods quite accurately as shown in Figs. 10A-F.

[0074] Figures 11A-D shows positions of part of the gp41 atoms surrounding the water molecule shown with arrows. The structure of gp41 is obtained from PDB (protein data bank) and is fixed throughout the calculation. The *ab initio* calculation of the protein-water interaction is performed to generate 1D potential curves by moving the water molecule with fixed orientation along the direction indicated by the arrows as indicated in Figs. 11A-D. Four different interaction paths were chosen as shown in Figs. 11A-D. These paths generally involve some form of hydrogen bonding or attractive interactions. The one-dimensional distances are defined as the distance between the two atoms at both ends of the arrows except for Fig. 11A in which the distance is defined between the oxygen atom of water and the center-of-mass of the protein that lies along the direction of the arrow. The orientation of the water is fixed as it moves along the one-dimensional straight path to generate potential energies as a function of distance.

[0075] The *ab initio* calculation is performed using Gaussian98 package. Quantum chemistry calculations were performed at several levels of theory, i.e., HF, DFT/B3LYP and

MP2. Figures 12A-D shows calculated 1D potential curves corresponding to the four different interaction paths illustrated in Figs. 11A-D. For comparison, the corresponding potential curves generated from AMBER force field were plotted in Figs. 12A-D. Figure 12A shows the potential curve obtained by HF/3-21G calculation in which the x-coordinate is defined as the distance between the oxygen atom of the water and the center-of-mass of gp41 (shown in Fig. 11A). Comparison of the *ab initio* potential curve with that from the force field in Fig. 12A shows that there are apparent differences between the two potential curves. The minimum position given by the force field is shifted outward by about 0.3 Å in addition to some quantitative difference in energy scales. However, the HF/3-21G level of *ab initio* calculation employs a small basis size and include no electron correlation. While HF/3-21G typically gives good equilibrium geometry, its calculated energy may not be very accurate, as is well known to those in the field. --

Please replace paragraph [0081] on page 23 of the Specification with the following replacement paragraph.

-- [0081]     The computational cost is reduced using the MFCC method. In the numerical test, such as that performed in Figs. 9A-F, a single point MFCC calculation using HF/3-21G method for the Gly-Ser-Ala-Asp-Val/water interaction system (with 62 atoms) takes about 2 minutes on a single processor Intel Pentium 1.5 GH linux workstation. In Figs. 11A-D, a single-point energy calculation of the gp41-water interaction system (with 985 atoms) at the HF/3-21G level takes about 67 minutes on a Pentium 1.5 GH PC running linux. With respect to correlated methods, the corresponding single point calculation takes about 516 and 518 minutes, respectively, using B3LYP/6-31G and MP2/6-31G methods. In fact, the MP2 calculation does not take as much time as had been expected for large systems simply because each individual MP2 calculation involving a protein fragment is still relatively small despite the large size of the protein. This demonstrates that one could actually employ high level electron correlation methods to do practical calculations for protein-molecule interaction energies beyond HF and DFT methods. --